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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/018,112	PETERSDORF ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,18,19,21-36 and 51-58* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11,21-36 and 51-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/14/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5-11, 18, 19, 21-36 and 51-58 are pending.
Claims 18 and 19 are withdrawn.
Claims 1-3, 5-11, 21-36 and 51-58 are examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 12/14/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

Information Disclosure Statement

1. The IDS of 12/14/2007 has been considered.

Withdrawn Duplicate Claims Warning

2. The duplicate claims warning regarding claims 25-27, 29-31, and 33-37 and the similar subject matter of claims 38-40, 42-44, and 46-50, as set forth in the previous Office Action, is **WITHDRAWN** in light of the cancellation of claims 38-40, 42-44, and 46-50.

Withdrawn Claim Rejections - 35 USC § 112 2nd – Indefiniteness

3. The rejections of claims 41 and 45 under 35 USC 112 2nd¶ presented in the previous Office Action are withdrawn in light of the cancellation of claims 41 and 45.

New Claim Rejections - 35 USC § 112 2nd – Indefiniteness

4. Claims 5 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 11 are dependent upon the limitations of claim 4, where claim 4 is a cancelled claim. It is thus unclear what the required limitations and the metes and bounds of the rejected dependent claims are, because the limitations of the base claim are cancelled.

Withdrawn Claim Rejections - 35 USC § 102

5. The rejections of claims under 35 USC 102 as anticipated by the prior art of Brennan (1995, US Patent 5,474,796), Apple et al (1995; US Patent 5,451,512), and Andrien et al (1994; WO 9421818), as set forth in the previous Office Action, are

WITHDRAWN in light of the amendments to the claims which require probes having (i.e. comprising) 17-23 nucleotides, and probes having a surface density within a particular range.

Withdrawn Claim Rejections - 35 USC § 103

6. The rejections of claims under 35 USC 103 as obvious in light of the teachings of Bettinotti et al (1997) in view of Sapolsky et al (1997, EP 0 785 280 A2); Bettinotti et al (1997) in view of Sapolsky et al (1997, EP 0 785 280 A2) and further in view of McGall et al (1995 US Patent 5,412,087); and Bettinotti et al (1997) in view of Sapolsky et al (1997, EP 0 785 280 A2) and further in view of Lockhart et al (1996 US Patent 5,556,752), are **WITHDRAWN** in light of the amendments to the claims to require range of probe surface density, and Applicants arguments (p.12-13 of Remarks) that the surface density of probes taught by Lockhart et is substantially different than the required surface density range of the claims.

While certain aspects of the teachings of some of the above cited prior art references (i.e.: Bettinotti et al and Sapolsky et al) are still applied in the maintained rejection in this Office Action, the remarks of Applicants that are pertinent to those teachings are addressed later in this Office Action in the appropriate Response to Remarks.

Maintained Claim Rejections - 35 USC § 103
As Necessitated by Claim Amendments

In the rejection of claims under 35 USC 103, the breadth of the claims is noted. The claimed array does not specifically require any particular probes of specific nucleic acid sequences. The claimed array requires only nucleic acid probes sufficient to represent a particular percentage of known polymorphisms in the HLA Class I locus, where the specification defines a known polymorphism as one that has appeared in the literature or available from a searchable database (page 15 of the instant specification). The claims are thus broadly drawn to an array requiring only probes sufficient to analyze a particular percentage of HLA polymorphisms.

7. Claims 1-3, 6-10, 21-36, 51and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettinotti et al (1997) in view of Sapolsky et al (1997, EP 0 785 280 A2) and Guo et al (1994; as cited on the IDS of 03/26/2007).

Bettinotti et al teaches the sequence analysis and typing of HLA-A, B, and C genes from samples of genomic DNA.

Regarding the limitations of probes comprising HLA Class I polymorphisms and particular percentages thereof, as set forth in claims 1-3 and 25, the reference teaches a database of the sequence of all known HLA-A, B, and C alleles (p.425 – Abstract; p.427, right col., lns.4-12). Thus the database of all known alleles comprises sequence information for HLA Class I region polymorphisms (relevant to claim 25) including at least 80%, 90%, and 98% of known polymorphisms in the HLA Class I locus, relevant to claims 1, 2, and 3, respectively.

Regarding the limitations of claims 6-8 and 26-28, the database of Bettinotti et al, which comprises all known HLA-A, B, and C alleles, because of its comprehensive nature, has sequence information pertaining to alleles of HLA-A, B, and C (relevant to claim 6, 26, 27). Relevant to claims 7, 8, and 28, the reference specifically teaches using the database in a comparison of the sequences of exons 2 and 3 (Fig 1; p.427, right col., lns.4-12) of HLA-A, B, and C.

Regarding the limitations of claims 21-24 and 29-32, the database of Bettinotti et al comprises sequences of at least 86 HLA-A polymorphisms (relevant to claims 21, 29), at least 185 HLA-B polymorphisms (relevant to claims 22, 31), at least 45 HLA-C polymorphisms (relevant to claims 23, 30), and at least 68 exon 2 and 70 exon 3 polymorphisms of HLA-B (relevant to claims 24, 32).

Bettinotti et al does not teach a microarray of oligonucleotides comprising a plurality of HLA Class I oligonucleotide probes.

Sapolsky et al teach a microarray of oligonucleotides for the detection of particular nucleic acid sequences. Relevant to arrays of the rejected claims, the reference teaches that an oligonucleotide array may comprise particular oligonucleotide probes complementary to particular polymorphic forms of segments of a nucleic acid sequence (e.g.: p.4. lns.23-29) and probes may encompass one or more polymorphic positions (e.g.: p.4 lns.47-48; Fig 3).

Regarding the limitations of claims 1, 25, and 33, Sapolsky et al specifically teach that an array for the analysis of nucleic acid sequences may be comprised of probes of 20 nucleotides in length (e.g.: Fig. 3; p.8, Example 1).

Neither Bettinotti et al nor Sapolsky et al teaches particular probe densities of probes on a microarray (as required by claims 1, 10, 25, 51, and 55), a microarray on a solid support that is a glass slide (claims 9 and 34), or oligonucleotide probes that comprise a linking group that is a 15-mer of poly-dT(35 and 36).

Guo et al teaches aspects of microarray fabrication for the analysis of nucleic acid sequences using probe hybridization.

Relevant to the recited probe density limitations of the claims (i.e.: about 250 to about 450 $Å^2$/molecule (claim 1); 250 to 450 $Å^2$/molecule (claims 10 and 25); 325 to about 375 $Å^2$/molecule (claims 51 and 55), Guo et al teaches creating arrays at various probe densities. Guo specifically teaches a probe density of 'approximately 500 $Å^2$/molecule' (p.5460, left col., ln.6-8), where a probe density of approximately 500 $Å^2$/molecule is about 450 $Å^2$/molecule as required by claim 1. Furthermore, Guo et al teaches the analysis of various probe densities specifically ranging from 2500 $Å^2$/molecule to 125 $Å^2$/molecule (i.e. Guo et al teaches that in analyzing probe density a 5mM oligonucleotide concentration corresponds to a surface density of approximately 500 $Å^2$/molecule, and Fig 3b shows data for oligonucleotide concentrations of 1, 2, 3, 4, 5, 7.5, 10, and 20 mM, and the teachings of p.5459, right col., lns.30-37 and Fig 3a that there is a linear relationship between oligonucleotide concentration and surface density). Relevant to the limitations of claims 10, 25, 51, and 55, the 7.5 mM oligonucleotide concentration, given the linear relationship asserted in Guo et al, corresponds to approximately 333 $Å^2$/molecule.

Relevant to claims 9 and 34, Guo et al teaches that microarrays of oligonucleotide probes were formed on glass (p.5457 – Preparation of ASO arrays on glass supports; p.5458 – Support chemistry)

Relevant to claims 35 and 36 Guo et al teaches that oligonucleotides covalently bound to a solid support (Abstract) may be comprised of a hybridization sequence and a spacer with 15 T nucleotides (Figure 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created an array of oligonucleotide probes, as taught by Sapolsky et al, using the sequence information of all of the known alleles of HLA-A, B, and C from a database as taught by Bettinotti et al. One would have been motivated to create such an array based on the assertion of Sapolsky et al that methods using such an array allow for the rapid, automatable analysis of nucleic acid sequences (p.1 – Abstract), and the teaching of Bettinotti et al that molecular testing for HLA typing by sequence analysis allows for higher resolution (p.425, left col., last paragraph). It would have been further obvious to incorporate the aspects of oligonucleotide microarrays specifically taught by Guo et al in the creation of an HLA Class I microarray according to Bettinotti et al in view of Sapolsky et al. One would have been motivated to use any probe surface density as taught by Guo et al, including probe surface densities in the ranges recited in the claims, based on the teachings of Guo et al that such densities allow for successful analysis of complementary nucleic acids (Fig 3b) and that different probe densities are optimal for different analytes (p.5460, left col., lns.1-14). One would have been motivated to use a glass slide as a solid support based on the teachings of Guo et al that such supports are an inexpensive support medium with a relatively homogenous chemical surface (p.5458 - Support chemistry). One would have been motivated to use the covalently bound probe structure of Guo et al (i.e. a linking group that is a 15-mer of poly-dT) based on the teachings of Guo et al that such a probe structure allows for efficient probe:target hybridization (p.5459, left col., lns.20-25; p.5460, left col., third paragraph; Figure 3d). One would have had a

reasonable expectation of success in combining the various elements of the cited references because all of the references teach the use of the various elements in the analysis of nucleic acid sequences requiring hybridzation.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 103 as obvious over the teachings of Bettinotti et al in view of Sapolsky et al. Applicants have argued (page 10 of Remarks) that to establish a *prima facie* case of obviousness requires teaching, suggestion, and motivation from the prior art to combine the required elements, and a reasonable expectation of success in combining the prior art elements. Initially it is noted that MPEP 2141 provides guidelines for determining obviousness in light of the recent decision by the Supreme Court in KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. ___, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that the Federal Circuit had erred by applying the teaching-suggestion-motivation (TSM) test in an overly rigid and formalistic way. KSR, 550 U.S. at ___, 82 USPQ2d at 1391. Thus it is noted that the Supreme Court ruling for KSR (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See Ex parte Smith (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007). The Examiner maintains that the rejected claims, broadly drawn to microarrays comprising oligonucleotide probes, are obvious to the artisan of ordinary skill in light of the teachings of the cited references.

the examiner maintains that the artisan of ordinary skill would be motivated to create the claimed array for the analysis of HLA sequences, as taught by Bettinotti et al,

using a structure that allows for efficient analysis of nucleic acid sequences, as taught by Sapolsky et al. And while Applicants assert that Sapolsky et al only teaches detection of single-bas polymorphisms, the Examiner maintains that such an interpretation of the teachings of Sapolsky is too narrow, where Sapolsky et al more accurately teaches the detection of any particular nucleotide sequence by probe hybridization. Thus while Applicants assert that the teaching of Sapolsky et al are not applicable to the highly polymorphic HLA loci, the examiner maintains that Sapolsky et al is applicable to the analysis of any known nucleic acid sequences, such as the HLA sequences taught by Bettinotti et al.

That Bettinotti et al does not describe probes to identify specific alleles (p.10 of Remarks) is not relevant, as it is the teachings of Sapolsky et al that provide for arrays of oligonucleotides for detecting specific nucleic acid sequences, where Bettinotti et al provide for the sequence information (i.e. a database of HLA Class I sequences).

With regard to Applicants' arguments concerning the reasonable expectation of success in the obviousness of the claimed method in view of the teachings of the prior art, the Examiner maintains that, as set forth in the rejection, the skilled artisan would have a reasonable expectation of success in combining the prior art elements to create the claimed array because the prior art teaches that all the elements may be used for the analysis of nucleic acid sequences using methods requiring oligonucleotide hybridization. Applicants have provided no evidence as to why the skilled artisan would no expect to be successful in combining the prior art elements. The Examiner maintains that there is a very reasonable expectation of success in combining the

elements of Sapolsky et al for the analysis of known nucleic acid sequences of the HLA Class I loci as taught by Bettinotti et al.

Applicants have further traversed (p.14 of Remarks) the rejection of claims based on the teachings of Guo et al with regard to the required probe surface densities of the claims. Applicants assert that the surface density of 'approximately 500 $Å^2$/molecule' is not sufficient to satisfy the density limitation of 'from about 250 $Å^2$/molecule to about 450 $Å^2$/molecule'. Initially, the Examiner maintains that the 'approximately 500 $Å^2$' satisfies the 'about 450 $Å^2$/molecule' portion of the limitations of claim 1, where the term 'about' allows for breadth in the required density. Furthermore, while Guo et al recites the specific density of 'approximately 500 $Å^2$', the skilled artisan would not ignore the other exemplifications of different probe surface densities as also taught by Guo et al, which provide for the successful use of probe densities ranging from about 2500 $Å^2$/molecule to about 125 $Å^2$/molecule, as set forth in the rejection. Thus Guo et al clearly provides for the particular probe surface densities required by the claims.

The rejection as set forth is **MAINTAINED**.

New Claim Rejections - 35 USC § 103

8. Claims 52-54 and 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bettinotti et al (1997) in view of Sapolsky et al (1997, EP 0 785 280 A2) and Guo et al (1994; as cited on the IDS of 03/26/2007), as applied to claims 1-3, 6-10, 21-36, 51and 55 above, and further in view of Brown et al (1998, US Patent 5,807,522).

The teachings of Bettinotti et al in view of Sapolsky et al and Guo et al are applied to claims 52-54 and 56-58 as they were previously applied to claims 1-3, 6-10, 21-36, 51and 55.

Additionally, relevant to claims 52, 54, 56, and 58, Guo et al teaches a linking group comprising an aminoalklysilane and a phenylenediisothiocyante (claims 52 and 56) where the phenylenediisothiocyante is 1,4- phenylenediisothiocyante (claims 54 and 58) (p.5457 – Preparation of ASO array on glass supports).

Bettinotti et al in view of Sapolsky et al and Guo et al does not teach spots of probes ranging from 100 to 150 microns in diameter (claims 52 and 56) or spots that are spaced with 400-500 microns separating the center of each spot.

Brown et al teaches aspects of microarrays of biological samples, including nucleic acids (Abstract; col.6 lns.1-25). Brown et al specifically teaches that an array may contain analyte-specific regions, which are spots (Fig 3) where each spot has a diameter between 20-200 microns and the spacing between spots, measured center-to-center is in the range of about 20-400 microns (col.9 lns.30-45).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the array of Bettinotti et al in view of Sapolsky et al and Guo, including an array with a linking group comprising an aminoalklysilane and 1,4- phenylenediisothiocyante, as taught by Guo et al, with spot diameters and separation distances as taught by Brown et al. The artisan of ordinary skill would be motivated to use the linker of Guo et al based on the teachings of Guo et al that such linker allow for the efficient coupling of oligonucleotides to solid supports

(p.5457 – Preparation of ASO arrays on glass supports; p.5458 – Support chemistry). The artisan with ordinary skilled could have performed routine experimentation within the spot diameter and separation ranges as taught by Brown et al to optimize such diameters and distances, including the diameters and ranges as recited in the claims and encompassed by Brown et al. The artisan of ordinary skill would be motivated to explore the spot diameters and separations to optimize array performance, and provide alternative reagents for the analysis of HLA class I loci, using routine optimization techniques known in the art.

Conclusion

9. No claim is allowable. No claim is free of the teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/